of radiation sensitivity. A subset of these candidate molecules could be validated having an impact in clinical outcome of radiation therapy treated HNSCC patients.

Conclusion: Our study demonstrates that multi-level radiation systems biology allows gaining deeper insights into chief mechanisms of radiation sensitivity, thereby paving the way for targeted individualised therapy approaches in radiation oncology.

Debate: This house believes that progress in the treatment of locally advanced NSCLC will come from:

SP-0102 Radiation treatment intensification

J. Belderbos[1]
[1]*Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Radiation Oncology, Amsterdam, The Netherlands*

A large proportion of non-small cell lung cancer (NSCLC) patients are diagnosed with locally advanced (stage III) disease. For this patient group the treatment of choice is definitive concurrent chemoradiation (CCRT). CCRT results in an improved overall survival (OS) compared to sequential chemoradiotherapy or radiotherapy alone because of improved locoregional control. However 2-year OS rates of 30-35% are still poor because many patients develop locoregional failures (about 30%) and distant metastases (about 40%)[1]. Currently locally advanced NSCLC patients selected for CCRT have FDG-PET scanning and imaging of the brain (MRI or CT scan). Despite this brain imaging with the present chemotherapy regimens used we are faced with the problem of brain metastases in about 10% of the patients within 1 year after chemoradiation.
In several chemoradiation studies it was reported that the Gross Tumor Volume is correlated with OS. This is rational since the tumor volume represents the number of clonogenic tumor cells that needs to be eradicated. To improve locoregional control the dose prescription could be escalated taking into account the individual Gross Tumor Volumes and tolerances using image guided adaptive Intensity Modulated Radiotherapy (IMRT). However there are radiation oncologists who challenge the usefulness of RT dose escalation and intensification in patients with stage III NSCLC. The outcome of a randomized phase III trial, RTOG 06171, revealed that NSCLC patients within the 74 Gy arm given in 7.5 weeks had worse local control and significantly worse overall survival as compared to the patients treated to 60 Gy arm in 6 weeks[2]. Patients in all study arms received two additional cycles of consolidation chemotherapy ± cetuximab. So the obvious question is: How do we continue?
Dose escalation with prolonged overall treatment time in NSCLC has previously been proven disappointing because of accelerated repopulation[3].In an individual patient data meta-analysis in patients with non-metastatic lung cancer, which included trials comparing modified radiotherapy with conventional radiotherapy, a significant OS benefit from accelerated or hyperfractionated radiotherapy was reported[4]. Another issue is the use of consolidation chemotherapy after concurrent chemoradiation. In the RTOG 0617 trial the increase in mortality started < 3 months after randomization during the period of consolidation paclitaxel-carboplatin chemotherapy. Generally taxanes given after RT increases toxicity and the combination of high dose to the heart and consolidation taxane-based chemotherapy might have caused toxic deaths and biased the outcome. RT dose intensification while using modern image guided adaptive IMRT and accelerated schemes is an important area of ongoing clinical research and should not be discontinued.
In Stereotactic Ablative Body Radiotherapy (SABR) much higher biologically equivalent doses are delivered compared to conventionally fractionated RT (typically EQD2 of 70-85 Gy), and has generated outstanding tumor control in early stage NSCLC. For SABR a significant dose–response relationship was observed for prescription EQD2 of 105 Gy or more (2-year LC 96%) or of less than 105 Gy (2-year LC 85%)[5]. Tumor size and overall treatment time were also important factors influencing outcome.
The tumor control probability of SBRT (small tumor volume) and conventionally fractionated chemoradiation (large tumor volume) were successfully described in a single model[6] suggesting that a dose-response relation in NSCLC does exist.
Recently there is a growing interest in genetic profiles that predict a patient's response to radiotherapy, because severe toxicity in a minority of patients limits the doses that can be safely given to the majority. Recent progress in genotyping raises the possibility of genome-wide studies. If we know the normal tissue reactions to radiotherapy by genotype we will really be able to tailor the individual radiation dose.
In conclusion: Besides the unsolved problem of the occurrence of distant metastases there is room for improvement of locoregional control in locally advanced NSCLC patients treated with chemoradiation. In the era of personalized treatment, radiotherapy dose intensification using image guided adaptive IMRT could be directed towards individual tumor volumes and tolerances. RT dose intensification while using accelerated schemes is an important area of ongoing clinical research

1. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:2181-90.

2. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *The Lancet Oncology* 2015; **16**(2): 187-99.

3. Machtay M, Hsu C, Komaki R, et al. Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non–small-cell lung carcinoma: Analysis of the Radiation Therapy Oncology Group (RTOG) experience. *International Journal of Radiation Oncology Biology Physics* 2005; **63**(3): 667-71.

4. Mauguen A,Le Péchoux C,Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol. 2012 Aug 1;30(22):2788-97. doi: 10.1200/JCO.2012.41.6677.

5. Kestin L,Grills I,Guckenberger M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol.2014 Mar;110(3):499-504. doi: 10.1016/j.radonc.2014.02.002. Epub 2014 Mar 11.

6. Selvaraj J, Lebesque J, Peulen H, et al. TCP modeling in a large cohort of NSCLC patients inclusive of geometric uncertainties ESTRO Forum 2015:S468 PO-0908

SP-0103
Better systemic therapy

J. Van Meerbeeck[1]
[1]*University Hospital Antwerp, Department of Thoracic Oncology-MOCA, Edegem, Belgium*

About one third of patients with non-small cell lung cancer (NSCLC) present with locoregional disease extension in either the mediastinum (T4) or the mediastinal lymph nodes (N2/3). Apart from a fraction in which resection after induction therapy is sometimes considered, selected patients with stage 3 are candidate for a so-called definitive radiochemotherapy, administered either sequentially or concomitantly. Despite staging with PET-CT scan and endosonographic mapping of mediastinal lymph nodes and notwithstanding a patient selection for this radical treatment, the outcome in stage 3 is nevertheless moderate with a median survival of 2 years [1]. Progression occurs after a median of 10 months and is due to local relapse or distant metastasis in 30 and 45% of cases, respectively. Any advance in the outcome in stage 3 NSCLC will hence depend on improvements in systemic therapy directed at distant metastasis. The past 10 years have seen important changes in the paradigm of treatment in selected patients with advanced NSCLC, in whom platinum-based doublet chemotherapy used to be the standard of care. The discovery of drugable genomic alterations has introduced precision medicine in oncology. Patients whose NSCLC harbour either an activating EGFR mutation, EML-ALK translocation or ROS1 amplification are now routinely treated with oral small molecule kinase inhibitors of the 1st, 2nd and 3rd generation instead of chemotherapy, with a significant improvement in outcome and a substantial impact on quality of life. Similar, although less pronounced effects have been observed when adding monoclonal antibodies directed at targets associated with angiogenesis or cell growth to the chemotherapy backbone. Unfortunately, the incorporation of these

'targeted' agents in current radiochemotherapy, either given concomitantly or as consolidation, was not successful with even detrimental results due to an increased toxicity and mortality. A lack of adequate patient selection based on the presence of the target biomarker may have contributed to these failures, as subgroup analyses suggest a benefit in target expressing patients. Trials are ongoing specifically addressing patients with stage 3 NSCLC and either an activating EGFR mutation or EML-ALK translocation. 2015 has seen the rapid implementation of immunotherapy in NSCLC treatment, with several monoclonal antibodies inhibiting checkpoint molecules showing superior outcome over 2nd line docetaxel. These agents will now advance in earlier stages and phase 3 trials with a consolidation strategy are ongoing. Controversial issues remain patient selection based on predictive biomarker expression, the combination of different checkpoint inhibitors and the risk of synergistic late pulmonary toxicity, when added to definitive thoracic radiotherapy. Although it is tempting to early implement promising new drugs in stage 3 treatment, caution should guide its sequencing within the radiochemotherapy backbone. Window of opportunity trials with induction treatment in biomarker selected patients will allow to explore the single agent activity and minimize the risk of additional toxicity.

1: Bradley JD et al. Lancet Oncol 2015; 16: 187–99

Symposium: Active surveillance for low risk prostate cancer: to treat or not to treat?

SP-0104

Does (very) low risk prostate cancer really exist?

F. Algaba[1]
[1]*Fundacio Puigvert, Barcelona, Spain*

Prostate cancer could be considered as insignificant or indolent (IPCa) when its presence does not bring about any risk for the life of the patient. If we start with this idea it is easy to understand that this situation is very difficult to predict since it depends on many variables of each patient, among which the life expectancy of the patient is one of the most important; therefore, it would seem to be a more theoretical question than practical, if it were not because it reflects an emerged reality by finding that up to 31% of the prostate carcinomas detected by high PSA serum levels, through study of the prostatectomy specimen, there were only small nodules of carcinoma that could have remained totally localized (latent) during the entire life of the patient, therefore they could have been treated with watchful waiting. It is clear that all of this supposition is a speculative exercise and only comes from indirect suppositions of the probable biology of a carcinoma node by its pathological characteristics. This fact explains that there are diverse definitions of IPCa in the radical prostatectomy specimens, although all coincide in requiring a small volume of tumor (< 5cc, although there is an author that accepts < 1cc), absence of aggressive Gleason patterns (no 4 or 5 patterns or Gleason score <7) and the majority also require, for a tumor to be accepted as indolent, to be a confined organ tumour with negative margins. In accordance with these criteria, the prevalence of IPCa varies between 2.3% and 31%, with an average of 18.3%. However, this uniformity of criteria is not the same at the time of determining the pre-operative model to predict IPCa, possibly because all the studies that try to correlate the extension of the prostate cancer in the biopsy with the volume in the prostatectomy specimen show that this correlation is very weak; and therefore, although all the needle biopsy criteria for defining an IPCa require the absence of an aggressive Gleason pattern (pattern 4 and 5 or Gleason score ≤ 7) would vary as regards the extension of the tumor in the cores (< 3 core with no core >50% of the surface, only one positive core < 3mm, 1% of all the cores, no core > 10% of the surface) and the inclusion between the criteria of the PSAD (PSA density). With all this variability the presumption of a possible IPCa in the radical prostatectomy specimen of the different authors has a sensitivity of 23% to 83.9% (average 53.2%) and a specificity of 61.9% to 99% (average 89.1%). Maybe it will help us to better identification of very low aggressive P.Ca patients the recent redefinition of Gleason patterns and the proposed grouping of prognostic grades. A new International Society Urogenital Pathology revision in November 2014 defined the current criteria with a precise definition of Gleason pattern 3 as small glands with variation in size and shape infiltrating amongst non neoplasic glands and Gleason pattern 4 according four different aspects as all cribriform growth (some of them previously considered as pattern 3), fused glands, ill defined glands and glomeruloid glands. But with the intention to improve the correlation with the clinical parameters a new grading system was. This new system follows the accepted the new Gleason patterns grouping them in five prognostic groups: Group 1 (Gleason 3+3), Group 2 (Gleason 3+4), Group 3 (Gleason 4+3), Group 4 (Gleason 4+4) and Group 5 (score Gleason 9 and 10). According this new arrangement an excellent correlation with the risk of biochemical recurrence we can obtain in needle biopsy and radical prostatectomy specimens.

Prostate cancer is considered insignificant (IPCa) when its presence does not bring any vital risk. IPCa in the radical prostatectomy is a small (< 5cc,), No Gleason 4 or 5, organ confined, negative margins. The average prevalence is 18.3%. The pre-operative model to predict IPCa is difficult. In the IPCa identification can help the new ISUP Gleason revision, pattern 3 small glands with variation in size and shape and Gleason pattern 4 according four different aspects as all cribriform growth, fused, ill defined and glomeruloid glands. A new system was accepted grouping them in five prognostic groups: 1 (3+3), 2 (3+4), 3 (4+3), 4 (Gs8) 5 (Gs9,10), with excellent clinical correlation .

SP-0105

The role of MRI in active surveillance

G. Villeirs[1]
[1]*Ghent University Hospital, Genitourinary Radiology, Ghent, Belgium*

T2-weighted MRI (T2w) typically shows a prostate cancer as a low signal-intensity area among the high signal-intensity normal peripheral zone tissue background. In the transition zone, prostate cancer has an equally low signal-intensity, although contrasting less well with the surrounding heterogeneous signal-intensity of glandular and stromal hypertrophy. It has been shown that the observed signal intensity inversely correlates to some extent with the aggressiveness of the cancer (lowest signal intensities in higher grade cancers). The sensitivity of T2w imaging for prostate cancer (of any Gleason grade) is quite high (up to 85%), but with a low specificity (about 55%) due to many false positive calls. Therefore, functional imaging tools are required to improve the overall diagnostic accuracy.

Diffusion-weighted MRI (DWI) is currently the most important functional technique in addition to T2w MRI. Its mechanism is based on the inhibition of spontaneous water diffusion in tumor areas, due to both increased cellularity (more hydrophobic cell membranes inhibiting water diffusion) and destruction of fluid-rich acini and ductules. Prostate cancers can hence be detected as areas of decreased signal-intensity on apparent diffusion coefficient (ADC) maps or as increased signal-intensity on high b-value images. It is more than noteworthy that a quite robust inverse correlation exists between ADC-values and tumor aggressiveness (lowest ADC-value in higher grade cancers).

Dynamic contrast-enhanced MRI (DCE) measures the amount and characteristics of tumoral neoangiogenesis. After an intravenous bolus injection of gadolinium-containing contrast media, prostate cancers tend to enhance earlier, more rapidly and with a more pronounced de-enhancement (wash-out) than benign or normal tissue. DCE greatly helps detecting cancers in the peripheral zone, but suffers from false positive calls in the transition zone due to similar enhancement characteristics in glandular hypertrophy.

Magnetic resonance spectroscopic imaging (MRSI) is a more advanced tool that currently is mainly performed in expert centers and in clinical trials. It is based on measurement of the relative concentrations of citrate and choline, markers of benign and malignant tissue, respectively. MRSI adds